

Comments and responses relating to the 1th draft risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds

Minor grammatical or spelling changes have been made without acknowledgment. Only substantial comments are listed.

Late submissions and comments from Japan, Australia and United States will be reflected in the next draft (27 April)

Table 1. Comments and responses relating to the third draft of the risk profile on perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds

General comments

Source of Comment	Page	Para	Comments on the first draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds	Response
Romania	12	41	Suggested text: There are no available experimental biodegradation data in water or soil for PFHxS. However, results for PFOS and PFOA used in a read-across approach indicate that PFHxS are not readily biodegradable. Biodegradation of the structural analogue PFOS have been evaluated in a number of tests in several studies. Aerobic biodegradation has been tested in activated sewage sludge, sediment cultures and soil cultures (ECHA, 2017a). Anaerobic biodegradation has been tested in sewage sludge. PFOS did not in any of these tests show any sign of biodegradation (UNEP/POPS/POPRC.2/17/Add.5). The very persistence (vP) of PFOA in water, sediment and soil has also been confirmed (ECHA, 2013). Since the stability of PFASs is in general based on the stability of the fluorinated carbon chain, it can also for PFHxS be concluded that no biodegradation can be expected in water, soil or sediment. Thus, it can be assumed that PFHxS are not biodegradable and is very persistent in water soil and sediment (ECHA, 2017a).	Text added
Romania	13	50	Suggested text: which is the longest of all perfluoroalkyl and polyfluoroalkyl substances (PFAS) for which data are available. It is also comparable to the longest human elimination half-lives recorded for known PBT/vPvB- and POP-substances such as some PCBs (ECHA, 2017a).	Text added
Romania	14	53	Suggested text: The highest concentration of PFHxS are found in blood, liver, kidney and lung. Urine is the primary route of excretion. Humans have a very slow elimination compared with other species, with an elimination half-life of 7 years or above. The	Text added

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			human elimination half-life of PFHxS is the longest of all PFAS and PFCAs for which there are available data, and comparable to the longest human elimination half-lives recorded for known PBT/vPvB and POP-substances such as PCBs. PFHxS have been shown to be transferred to the foetus through the placenta in humans and excreted via lactation. Transfer to breast milk appears to be a significant route of elimination during breastfeeding. Time trend studies indicate that the human bioaccumulation potential of PFHxS may be larger than that of PFOS (ECHA, 2017a).	
Romania	16	62	Consider to add sentence: In blood serum of some office workers in Boston, exposed to FTOHs, PFHxS reached 0.2-13 ng/mL with of geomean of 1.5 ng/mL (Fraser et al., 2012). Fraser AJ, Webster TF, Watkins DJ, Nelson JW, Stapleton HM, Calafat AM, Kato K, Shoeib M, Vieira VM, McClean MD (2012). Polyfluorinated Compounds in Serum Linked to Indoor Air in Office Environments. Environmental Science & Technology, 2012; 46: 1209-1215.	Data will be added to the INF document.
Romania	18	Section 2.4	It should be mentioned somewhere here that even though PFHxS can induce toxic effects, it is concluded that the toxicity data available are not sufficient for classification for reprotoxicity or for specific target organ toxicity after repeated exposure, to cover the request of Annex E letter (f) on the issue of hazard classification	Information related to Annex E f) is summed up in Section 1.4.
Romania	21	95	In my opinion this paragraph belongs to section 2.2.3 on Bioaccumulation	Comment noted, but no changes made to the text as it might be helpful for the reader to be informed that the top predator in Arctic is heavily contaminated when this paragraph is about cocktail effects.
Romania	21	Section 3	Looking at previous draft risk profiles (e.g. PFOS, decaBDEs), usually under this section it was included a summary table on POP characteristics of the analysed substance; maybe it would be useful to have such summary table on PFHxS POPs characteristics here too	A summary table has been added.
Sweden	15	61	ng/kg is a strange unit for serum.ng/L?	Checked reference and corrected to ng/g wet weight
Sweden	15	61	Serum ? If so see comment above.	Checked reference and corrected to ng/g wet weight
Sweden	18	77	Suggested text: The exposure caused hepatomegaly with steatosis as well as reduced serum total cholesterol and triglycerides (Bijland et al., 2011). The authors hypothesise that PFHxS impaired lipoprotein secretion from the liver, leading to accumulation of lipoproteins and triglycerides in the liver,	Text has been rephrased.

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			causing hepatomegaly and steatosis, and reduced serum lipoproteins and triglycerides.	
Sweden	19	80	Suggested to move this sentence: A NOAEL of 0.3 mg/kg bw/d was shown for hyperplasia of thyroid follicular cells. Some mechanistic studies have explored the effect of PFHxS on the thyroid hormone pathway.	Done.
Sweden	19	83	Comment: Since this section is related to thyroid effects I suggest to put it under section 80 (i.e. become section 81).	Done.
Sweden	19	84-85	Comment: The value of the information in these sections could in our view be considered. If kept perhaps move it under 2.4.3 and para 88 ?	We prefer to keep this information in the terrestrial section as we only have human epidemiology studies in 2.4.3. We also believe it is important to keep information on specific mechanistic effect observed for this substance since the number of controlled in vivo studies are so limited.
Sweden	23	107	Comment: Since the liver is highlighted in the summary as well as in the results I think it should be mentioned here too.	Added
UK	General comment		<p>Since the risk profile is only a summary, it is very difficult to tell what level of critical review has been carried out for each of the cited studies. A reader will therefore assume that all of the information presented is fully valid and carries equal weight, regardless of its overall quality and reliability. Hopefully this type of analysis will be more clearly presented in the accompanying background information (including Klimisch or CRED scores). This particularly applies to new studies that have not been previously seen by regional expert groups (e.g. published in 2017/8).</p> <p>For toxicity studies, we should also be cautious about accepting the results of academic studies that do not conform to standardised test guidelines, and these need particularly close scrutiny.</p> <p>The stated effects in mammalian systems (e.g. paragraph 8 of the Executive Summary) may or may not be a concern. It depends on the degree of change, doses at which they occur (including whether a threshold exists, or not), and also a judgment about whether a reported effect (e.g. 'lipid protein metabolism') is significantly adverse. We are not in a position to make this analysis as we would need to seek input from human health toxicologists, and there has not been sufficient time to do this.</p> <p>As an example of how this sort of information could be misconstrued, paragraph 9 of the Executive Summary clearly states that PFHxS is "toxic to animals and humans". However, in an EU context, there was no agreement that this substance meets the "Toxic" criterion of Annex</p>	<p>All paper referenced are peer reviewed literature and have therefore gone through a review process. The way the risk profile for PFHxS is written is normal procedure and according to the Annex E criteria of the Stockholm Convention. The risk profile is limited to around 20 pages and contains only a review of the criteria to be covered under Annex E and this is very different from the PBT-process (or restriction process) under REACH. Under the Stockholm Convention there is no requirement to use standardised test guidelines such as OECD-guidelines for the data presented. The information document (supplementary information) (first draft distributed with the 2nd draft of the risk profile) only contain tables with data (especially concentration levels in a variety of matrixes). The supplementary document will only be available in English hence for transparency reasons the document will only contain table with numbers.</p> <p>Regarding comment on paragraph 9 of the Executive Summary clearly states that PFHxS is "toxic to animals and humans"; this statement is based on results presented in the present risk profile of PFHxS and according to the criteria under the Stockholm Convention.</p> <p>Concerning the statement on toxicity in the REACH annex XV dossier : This dossier concentrated on persistence and</p>

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			XIII of the REACH Regulation when this was formally discussed at the European Chemicals Agency in 2017.	bioaccumulation and did not do any thorough review of the toxicity studies available.
UK	6		Table 2, page 6 (physicochemical properties): Some statement should be made about the reliability of the estimated data (e.g. in terms of the appropriateness of the QSAR or read-across that has been used). How do they compare with other data for related substances (e.g. PFOS, for which measured data may be available for some of these end points)?	Text added See also comment above.
UK	7	25	Section 2.1 (production, etc.), paragraph 25, page 7: Information on amounts appears to be over ten years old. It is important to obtain a more reliable estimate of production quantities (both primary manufacture and as an unintentional by-product in other materials). Is there any potential for the secretariat to write to the listed companies to ask them for information?	We have recently had a consultant contacting as many as 53 global stakeholders. There has been no willingness to release the information that you are asking for. Please see "Investigation of sources to PFHxS in the environment (M-961/2018)" that is now referenced in the RP.
UK	10 and 11	29 and 36	Section 2.1.2 (uses), paragraph 29, page 10 and paragraph 36, page 11: Given the strength of the C-F bond, we are surprised at the claimed use as a flame retardant, and wonder if this is a mis-translation of the fire-fighting use. Perhaps this could be double-checked with the company? – if it is confirmed then it would be important to understand what types of material may be flame retarded using this substance. We are aware of some use of PFOS as a pesticide active substance, so that is less of a surprise – although as this is potentially a wide dispersive application further information would be useful.	This information is according to the company's web page and the recommended/possible use of the substances they sell. Regarding the possibility to get any information from stakeholders see comment above.
UK	11	38	Section 2.1.3 (releases), paragraph 38, page 11: We do not know whether the levels being detected in remote environments are a result of historical or current use. It would be helpful to present a ranked comparison of likely releases from different uses (even if only quantitative) – if possible (e.g. by analogy with PFOA and PFOS) – since this would help to establish their priority for risk management. If there is going to be an approach to the industry at some point, perhaps they should be asked to provide more reliable information on releases at the same time.	We are not able to do this with the information we have available today. We have been in contact with possible producers and there has been no willingness to provide information on production, use and release or other information requested. Regarding the possibility to get any information from stakeholders see comment above
UK	14-15	53-57	Section 2.2.4 (potential for long-range transport), paragraphs 53-57, pages 14-15: It would be helpful to mention concentrations in this section together with some comparison with data for agreed POPs, to provide context. Also, if there are likely to be local sources (mentioned in paragraph 54), it would be useful to more clearly describe what these are, and their relative magnitude compared to others. If possible, can the quantities of PFHxS being deposited annually in the Arctic be estimated (e.g. are we talking kilograms or tonnes?).	Regarding the magnitude of local sources compared to long range transport sources, there are no good methods available to distinguish between the two. But text has been added to reflect exposure to polar bears at Svalbard. We are working on adding more data to the INF document and we will consider having a table comparing levels of PFHxS and listed POPs. The supplementary document (INF document) will contain concentrations observed in the environment and humans,

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				and we will try to use consistent units as far as possible.
UK	15-18		Section 2.3 (exposure), pages 15-18: Again, some indication of concentrations would be helpful, perhaps pictorially in a graph? This could also be used to visualise the time trend information. Where concentrations are mentioned, it would be good to use consistent units (e.g. human blood serum/plasma levels are reported in terms of both ng/mL and µg/L – these are the same so one should be used for consistency).	See comments above.
UK	18	76	<p>Section 2.4.1 (toxicity to aquatic organisms), paragraph 76, page 18: It would be helpful to report the outcome of standard toxicological tests (if they exist), and any data gaps, in this section.</p> <p>We have not had time to retrieve the Hoover et al. (2017) or Lou et al. (2013) references, but the reported findings for amphibians may be of concern if the studies are reliable.</p> <ul style="list-style-type: none"> Although PFHxS was “more potent” than PFOS in causing developmental effects in <i>Rana pipiens</i>, it would be helpful to know the degree of change, etc. We note that the published abstract recommends that the effects “<i>merit further study</i>” and it would be useful to know the reasons (e.g. was the study design less than ideal?). The description of the <i>Xenopus laevis</i> study states that “<i>both PFOS and PFBS... caused adverse effects on sexual development and hepato-histology at high concentrations (100-1000 µg/L)</i>”. It would be useful to know what type of liver impairment was observed, and whether this is toxicologically relevant. However, the paper’s abstract states that “PFBS had no effect on the sex ratio and gonadal histology”, so the statement made in the draft is misleading (i.e. it appears that estrogen (ER) and androgen receptor (AR) expression was promoted, but sex hormone concentrations do not seem to have been measured, and therefore the abstract says there were only “potential” effects on sexual development). Again, the abstract highlights a need to “<i>further study effects of PFOS and PFBS on subsequent gonadal development, sexual dimorphism, and secondary sex characteristics</i>”, which could imply that the study is less conclusive than it might appear. [The units for PFHxS levels in the PFOS study (g/L) appear to be incorrect.] <p>In both cases, it would be good to know whether the evidence is definitive and</p>	<p>It is stated in the first line that available studies for toxicity to aquatic organisms is limited.</p> <p>We have not come across any standard aquatic toxicity test for PFHxS-substances. This is why we have referred to studies including both C4 and C8-fluorinated sulfonate to indicate what to expect for the C6- sulfonate.</p> <p>We have included relevant peer-reviewed literature to illuminate possible concern.</p> <p>Some more details about the amphibian studies have been added for clarification, and wording revised.</p> <p>Units for PFHxS in the PFOS study has been corrected.</p>

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			conclusive, or just indicative of a possible adverse effect that needs further clarification.	
UK	18-20	77-88	Section 2.4.2 (toxicity to terrestrial mammals), paragraphs 77-86, page 18-20: It would be helpful to report the outcome of standard toxicological tests (if they exist), and any data gaps, in this section. As noted in our general comments, we would need to seek views from a mammalian toxicologist to better understand whether the reported effects are reliable and relevant.	We have used the available peer-reviewed studies that we have been able to identify.
UK	19	86	The opening three sentences of paragraph 86 (page 19) on levels in Polar Bears appear more relevant for the bioaccumulation/long range transport sections than the toxicity section. We have some concerns about the interpretation of the studies that found correlations between PFCA/PFAS levels and neurotransmitter markers, and in particular the statement “ <i>PFAS concentration[s] in polar bears from East Greenland have exceeded the threshold limit for neuro-chemical and hormonal alterations</i> ”. These studies are not specific to PFHxS, and we do not know the condition of the bears (or how many were examined), whether “controls” were considered, or what other substances the animals had been exposed to (presumably several POPs and other substances that were not measured, which might include organophosphates, for example). If there are no standard mammalian studies showing a clear connection between PFHxS exposure and the purported “effects”, we think this statement should be removed. If there are links with other studies, then these should be referred to more clearly in the narrative of this paragraph. Similarly, the statement that “ <i>PFAS contribute to alteration of the thyroid hormone homeostasis in polar bears</i> ” seems too strong – there is an apparent correlation, but nothing to explicitly confirm a relationship between actual thyroid effects and PFHxS in this species.	We agree that the sentence could fit into the bioaccumulation/long-range transport section, but prefer to keep it here to give some perspectives of distribution of PFAS in the polar bear since the correlation studies were done in the brain. The text has been edited.
UK	20-21	87-92	Section 2.4.3 (human toxicity), paragraphs 87-92, page 20-21: As noted in our general comments, we would need to seek views from a mammalian toxicologist to better understand whether the reported effects are reliable and relevant.	Comment noted.
UK	21	94	Section 2.4.4 (mixture toxicity), paragraph 94, page 21: This paragraph is not helpful – what end points were examined, are they toxicologically relevant, and what substances were involved in the binary mixtures, at what concentrations?	Comment noted, the text has been edited.
UK	21	95	Section 2.4.4 (mixture toxicity), paragraph 95, page 21: How was lipid metabolism measured by Tartu et al (2017a) (was this an <i>in vitro</i> study or an inference based on blood analysis)? Without further background information, it is not possible to assess the validity of the conclusion that “ <i>PFAS and other</i>	Details have been added for clarification concerning lipid metabolism endpoints. This paragraph tries to summarize the mixture toxicity concern for Arctic top predators, which are highly exposed to certain PFASs, several POPs and other chemicals with POP characteristics

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			<i>organohalogenated compounds have a synergistic negative effect on Polar Bears</i> ".	
UK	23	103 - 104	Section 3 (synthesis of information), paragraphs 103-104, page 33: These two paragraphs summarise reported "effects of PFHxS" either alone or in mixtures. As noted above, we have some concerns about the reliability of some of the statements that have been made in this draft. In particular, the quality, reliability and relevance of the various cited studies is unclear, and the reported perturbations of the endocrine system are not based on a robust weight of evidence analysis.	Comment noted. All data included in the risk profile are peer-reviewed data. No changes were made to the text.
UK		103	We note that the final sentence of paragraph 103 states that the immune system is 'particularly' vulnerable to PFAS and PFHxS exposure " <i>observed as associations between serum PFHxS levels and reduced effect of vaccines and higher incidences of infections ... in children</i> ". However, the draft document does not describe any studies about vaccines or infections, and as there is only a correlation with asthma with no description of co-exposure to other compounds or confounding factors and no further supporting evidence from mammalian studies, we do not think a statement about "particular vulnerability" should be made.	Comment noted, text has been edited. This is referring to paragraph 88, new paragraph 95 and the effects on vaccination observed in: Granum et al., 2013; Grandjean et al., 2012; 2017, and the effects on infections observed in: Granum et al., 2013; Goudarzi et al., 2017.
UK	33	107	Section 4 (concluding statement), paragraph 107, page 33: We agree that there are concerns for people who have been exposed to high levels of PFAS (including PFHxS) via contaminated drinking water. It is much less clear whether there is a likelihood of adverse effects in wildlife populations or individuals at the lower concentrations that are found in remote regions. For example, this paragraph talks about "possible alteration in thyroid hormones" in Polar Bears, which is a more measured statement than some of the firmer ones made in the preceding sections. We are also missing any comparison of levels in wildlife and the concentrations that have led to the purported adverse effects in the laboratory (with or without safety factors).	Comment noted. PFHxS is a highly bioaccumulative and persistent compound, and certain animals as the polar bear are extremely polluted by several POPs including PFHxS and other PFASs. Levels observed in the environment will be provided in the INF-document.
UK			So, whilst we agree that PFHxS is highly persistent and has bioaccumulative properties of concern, we would like to see a more transparent description of the adverse effects and comparison with exposure levels before we would agree that there is a significant risk to wildlife.	Comment noted. There is no requirement under the Convention to compare relevant environmental levels and adverse effects. Lastly Article 1 of the Convention states that "Mindful of the precautionary approach as set forth in Principle 15 of the Rio Declaration on Environment and Development, the objective of this Convention is to protect human health and the environment from persistent organic pollutants." Article 7, paragraph 8 (a) moreover states that "Lack of full scientific certainty shall not prevent the proposal from proceeding."

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IPEN/ACAT	3	2	used as PFOS alternatives in	No changes made. There is no good reference to usage of PFHxS as a PFOS alternative.
IPEN/ACAT	4	12	used as PFOS alternatives in	Some text has been added to para 12
IPEN/ACAT	10	29	PFHxS was produced as an alternative to PFOS and later considered to be undesirable due similar environmental and health hazards. To be added before: Due to the thermal and chemical stability as well as the hydro- and oleophobicity of the perfluoroalkyl....	No changes made. Again there is good reference to usage of PFHxS as an alternative to PFOS, some of which still occurs, in the document.
IPEN/ACAT	11	37	industrial or consumer use, as well as from waste treatment facilities such as landfills and wastewater treatment plants (including from land treatment using contaminated sludge from wastewater treatment plants). Please add after this: Studies indicate that PFHxS remain relatively unchanged throughout the successive treatment steps. Furthermore	Addressed
IPEN/ACAT	11	38	levels of PFHxS in water and the population close to a production plant in Minnesota, the US (Oliaei et al., 2012). Please then add: In recent years Fuxin City has become the main fluorochemical industry center in North China, leading to several reports of high contamination in the surrounding environment (see e.g. Zhu, et al. 2015 and Bao, et al. 2017). High levels of contamination from manufacture have also been reported in Shanghai, Wuhan and Taiwan.	Some has been addressed in the INF document and some directly in the text. Unfortunately we do not have access to a number of the papers in your submission.
IPEN/ACAT	13	44	1. Please add to end: Perfluorooctane sulphonamide is taken up by wheat (<i>Triticum aestivum</i> L.) and degraded to PFHxS and perfluorobutane sulfonate (PFBS.) N-ethyl perfluorooctane sulfonamid is a PFOS precursor used in sulfluramid and taken up by wheat (<i>Triticum aestivum</i> L.), soybean (<i>Glycine max</i> L. Merrill) and pumpkin (<i>Cucurbita maxima</i> L.) in hydroponic growing systems and degraded to perfluorooctane sulphonamide acetate, perfluorooctane sulphonamide, PFOS, PFHxS and PFBS. A study of influent and effluent sewage water and sludge from waste water treatment plants found that the presence of precursor PFAS resulted in a net mass increase in PFHxS, suggesting that degradation of precursor compounds can be a significant contributor to PFAS contamination in the environment.	Not relevant in this context: Zhao S, Zhou T, Zhu L, Wang B, Li Z, Yang L, Lui L (2018) Uptake, translocation and biotransformation of N-ethyl perfluorooctane sulfonate (N-EtFOSA) by hydroponically grown plants, Environ Pollut 235:404-410 Eriksson et al 2017 is reflected in section: 2.2.2 PFHxS precursors and degradation
IPEN/ACAT	17	64	Please add at end: A study using data from the US National Health and Nutrition Examination Survey for 2013 – 2014 for children aged 3 – 11 years-old (n=639) found that higher levels of PFHxS in serum were associated with consumption of fruits and juices.	Information added.
IPEN/ACAT	17	67	Please include after first sentence: Of 17 PFCs measured in house dust, Kato et al. 2009 detected PFOS, PFBuS, and PFHxS at the highest median concentrations followed by Et-PFOSA-AcOH and Me-PFSA-EtOH.	Information will be included in the INF-document.

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IPEN/ACAT	18	68	Please add at end: Hanssen et al. 2013 detected PFHxS in every sample of maternal and umbilical cord whole blood and plasma in a study of women and their newborn children (n=7) from Arctic Russia. In an analysis of data from the 1999-2006 National Health and Nutrition Examination Surveys (NHANES) of 1,043 participants aged 60 and older in the U.S. population, the authors found that levels of PFHxS were above the LOD in greater than 90% of the participants.	Hanssen et al has been included in the risk profile, and data from Fry et al 2017 will be included in the INF-document.
IPEN/ACAT	18	69	Please add after (Tao et al. 2008). Ye et al. quantified serum concentrations of PFHxS in a nationally representative subsample of 639 3–11 year old participants in NHANES 2013–2014 and detected PFHxS in all children, suggesting prevalent exposure despite most of them being born after the phase out of PFOS in the United States in 2002.	Information has been added.
IPEN/ACAT	19	72	Please add at end: In a longitudinal study of men conducted in Northern Norway, concentrations of PFOS and PFOA were highest during 1994–2001 and 2001, respectively, whereas PFHxS levels increased to 2001, however did not decrease between 2001 and 2007.	Text has been added.
IPEN/ACAT	19	74	In the Fu et al. 2016 study serum concentrations of PFHxS were in the ranges of < LOD to 19,837 ng mL⁻¹ (median = 764 ng mL ⁻¹). The serum levels of PFHxS in the exposed workers showed an obviously increasing trend with length of service. Concentrations in urine ranged from <LOD-77.1 ng mL ⁻¹ (median=1.7 ng mL ⁻¹)	Text has been added.
IPEN/ACAT	21	85	Please add at end: In a study of polar bear mothers and cubs from Svalbard, PFHxS levels did not decline between 1998 and 2008, with levels exceeding those associated with health effects in humans, including neurobehavioral effects and alterations in serum cholesterol.	Text has been edited.
IPEN/ACAT	21	86a	Please add at end: A study of 1240 pregnant women from the Spanish Environment and Childhood Project found that PFOS and PFHxS were positively associated with impaired glucose tolerance and gestational diabetes mellitus.	Text has been added.
IPEN/ACAT	21	86b	Please add at end: In a study measuring prenatal concentrations of PFHxS in serum collected from pregnant mothers at enrollment (1991–1992) in the Avon Longitudinal Study of Parents and Children (ALSPAC), results indicate that prenatal exposure to some PFAAs may alter testosterone concentrations in females.	The linear regression between serum PFHxS levels and serum testosterone is not showing a convincing trend in this study, and without any other studies of more convincing data we are reluctant to take this study into the risk profile. No changes were made to the text.
IPEN/ACAT	22	87	Please add at end: Among 83,389 mother–child pairs enrolled in the Danish National Birth Cohort during 1996–2002, there was evidence of a positive association between PFHxS and autism (Liew, et al. 2015).	Text has not been added due to the weakness or non-conclusive effect shown for PFHxS in this study.

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IPEN/ACAT	23	88	Please add at end: A prospective birth cohort study of 1056 woman found that prenatal exposure to PFOA, PFDA, PFDOA and PFHxS significantly increased the risk of childhood atopic dermatitis in female children during the first 24 months of life.	Text has been added.
IPEN/ACAT	23	89	Please add at end: Also, Lee et al. analyzed the concentrations of PFHxS in maternal and umbilical cord sera at delivery from the general population in Korea. Umbilical cord PFHxS concentration showed a significant inverse association with birth weight or a marginally significant inverse association with birth length.	Text has not been included now, we will try to make a table for the INF-document summarizing the all identified studies on birth effects for transparency, and this study will be included there.
IPEN/ACAT	23	90	Please add at end: In a case-control study of the relationship between serum levels of certain POPs and risk for breast cancer in Greenlandic Inuit women, Wielsoe et al. found a significant positive association between breast cancer risk and PFHxS.	Text has been added.
IPEN/ACAT	24	95	Please amend to: PFHxS belongs to the perfluoroalkyl substance (PFAS) group and has been used as a substitute for PFOS in surfactants, water- and stain protective coatings for carpets, paper, leather and textiles and in fire-fighting foams among other applications. It is also known that PFHxS can be unintentionally produced during the electrochemical fluorination processes used in production of other PFAS e.g. PFOS. These compounds have provided surfactant, water- and stain protective functions in various products due to their thermal stability and hydrophobic and lipophobic nature.	Text has been edited.
FluoroCouncil	General comment		The term “PFAS” is often used incorrectly – either “PFSA” is meant or “specific or certain PFAS” are meant. Please make sure when you go through the document to highlight and correct these. Furthermore, I suggest we insert language - where appropriate - that PFHxS is considered a long-chain PFSA substance according to the OECD definition (and provide a link to the website). Thirdly, throughout the document substances are mentioned with their CAS # only without providing background on chemical identity. Please check all these CAS # to ensure the substances are in-scope and suggest including all these in Table 4 and some of these in Figure 1 so that a cross-reference with the chemical inventories can be made.	Text has been edited where appropriate. We have tried to be more specific in the use of PFAS throughout the text. We have added chemical names in the text that had only CAS no.
FluoroCouncil	5	16	Please check this sentence for accuracy. It is not clear that a strong acid provides both water- and oil repellency: "Perfluorohexane sulfonate (PFHxS) is a strong acid with a fully fluorinated six carbons long chain, making it both oil- and water repellent "	Text has been edited.
FluoroCouncil	7	22	This is somewhat unclear. The precursor substance for PFOS is PFOSF:	Text has been edited

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			Similarly to PFOS, its salts and PFOS-related compounds, perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds have been produced from the same parent compound, perfluorohexane sulfonyl fluoride (PFHxSF).	
FluoroCouncil	9	Table 4	Comment to Table 4: It will help the interested reader if some of the key substances listed here will be shown as examples in Figure 1.	No changes made to Figure 1. Annex I in Supplementary document contain all the CAS no, chemical names and chemical structures.
FluoroCouncil	10	32	Please add word in red: The industrial activities with C-6-sulfonate waterproofing agent for textiles in the Taihu Lake region in China might be a potential source of PFHxS where recent production and use of PFHxS as an alternative to PFOS and PFOA has been reported (Ma et al., 2017).	No changes made to the text. The text reflects the text in the peer reviewed paper.
FluoroCouncil	12	46	Please avoid using the term short-chain within this context as it may be confusing. PFHxS is <u>not a short-chain</u> compound : http://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/aboutpfass/	Text has been edited as requested
FluoroCouncil	15	60	Please provide the CAS # for this substance and please cross reference with Table 4.: form of perfluorohexane sulfonamide (FHxSA)	No such information is provided in the referenced literature. FHxSA refers to the group of perfluorohexane sulphonamides detected by non-target analysis.
FluoroCouncil	17	68	Please consider including descriptive text from the following human biomonitoring data references : “Fourth National Report on Human Exposure to Environmental Chemicals”, February 2015, Updated Tables, Volume Two, January 2017, US Centers for Disease Control and Prevention. https://www.cdc.gov/exposurereport/index.html “Second report on human biomonitoring of environmental chemicals in Canada», Government of Canada Publications, Health Canada, 2013 http://publications.gc.ca/site/eng/442162/publication.html Stuart Wuttke, Elsa LaCorte, Diego Garcia, and Maria Ooi. First Nations Biomonitoring Initiative: National Results (2011). Assembly of First Nations, 2013 http://www.afn.ca/uploads/files/afn_fnbi_en.pdf	We will incorporate data in the INF document for levels in humans, and also incorporate some lines in the risk profile for the next draft. At the moment we have had some problems with downloading the documents for the first link.

Source of Comment	Page	Para	Comments on the first draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds	Response
			<p>“Concentrations of Selected Persistent Organic Pollutants (POPs) in the Serum of New Zealanders»,</p> <p>Technical Report No. 34 A report for the Ministry of Health, Wellington Prepared by the Centre for Public Health Research (CPHR), Massey University, Wellington, 2013</p> <p>http://publichealth.massey.ac.nz/assets/Projects/PDF/Concentrations-of-Selected-POPs-4-October-2013-FINAL.pdf</p>	
FluoroCouncil	17	69	<p>Please specify correctly. POPRC14 is scheduled for the Fall of 2018 and has not taken place:</p> <p>Table XX in POPRC14/INF/XX</p>	This refers to the INF document to be presented at POPRC14. This INF document will contain supplementary information in tables only and is to be distributed together with 2 nd draft of the PFHxS risk profile.
FluoroCouncil	20	87	<p>Please insert reference to these studies: The National Health and Nutrition Examination Survey (NHANES),</p> <p>(Nelson et al., 2010)</p>	Added
FluoroCouncil	20	88	<p>Please insert reference to these studies: The National Health and Nutrition Examination Survey (NHANES),</p> <p>(Jain et al. 2013)</p>	Added
FluoroCouncil	20	88	<p>It is unclear what substance is meant here: PFHA</p>	Corrected to PFNA
FluoroCouncil	21	89	<p>Please include the references to these studies.</p> <p>National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2003-2004,</p> <p>(Hoffmann et al., 2010)</p>	Already in the draft RP
FluoroCouncil	21	92	<p>Please include reference to these studies.</p> <p>U.S. population in NHANES 2009-2010 (Khalil et al., 2016)</p>	Added
The Netherlands	General comment		<p>The risk profile is well-written and goes back to the original sources in most cases. I would like to compliment the drafters doing that as it makes tracing back the information much easier.</p> <p>The profile aims at providing the POP Review Committee with scientific information with which a considered opinion can be made on adding PFHxS to the convention. Such information should contain scientific data rather than generic statements on all kinds of PFCs. Thus, I would recommend to skip such generic statements as much as possible and to keep the text to PFHxS. I further observe that the risk profile incorporates estimations or statements made in scientific reports, but lacks the incorporation of critical statements made by the same scientists, which impede a correct interpretation by POPRC. Examples are the remarks made on precursors by Claus Nielsen in the report of the Norwegian Environmental</p>	<p>Due to the page limits, drafters are forced to make a review of results presented in the referenced literature. We are trying to do this in as balanced way as possible. However, we cannot include every statement of reservations to the results made in the articles.</p> <p>We trust that the POPRC members know the complexity of extracting information from field studies. We also try to incorporate peer-reviewed studies that we consider reliable, and avoid studies with obvious bias.</p> <p>For this complex group of substances it is sometimes necessary or unavoidable to include information about the PFAS group and not only on PFHxS.</p>

Source of Comment	Page	Para	Comments on the first draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds	Response
			Agency (2017) and remarks of the Swedish EPA (2017) and Butt et al (2008) on bioaccumulation.	
The Netherlands	General comment		<p>In my opinion the risk profile should also indicate where the substance meets the criteria and where it does not and, if possible, why. In para 2.2.3 the profile reflects that PFHxS does not meet the bioaccumulation criteria and why that is the case and subsequently continues with the topics that are considered relevant for the bioaccumulation criterium, excellent. However, such an approach is lacking in the toxicology section. When there are data, either positive or negative, it should be reflected in the profile. The fact there there is no classification for carcinogenicity (IARC), and there are no classification on aquatic toxicity should be mentioned clearly in the sections on human and eco-toxicity. Swedish EPA (2017) concludes in their annex XV report for REACH: Although PFHxS can induce toxic effects, it is concluded that the toxicity data available are not sufficient for classification for reprotoxicity or for specific target organ toxicity after repeated exposure in category 1 (STOT RE1). This should be reflected as well in the section on human toxicity. I consider classifications as a starting point in our exercise. If they are not present, or if there is a conclusion that the data are not sufficient enough, it may signal POPRC in their decision. I also note that such information is not reflected in the executive summary.</p>	<p>A table summarizing how the POP criteria have been met is now included under "Synthesis of information".</p> <p>However, the REACH annex XV dossier concentrated on persistence and bioaccumulation and did not do any thorough review of the toxicity studies available.</p> <p>Regarding the comment on lack of classification for PFHxS - we do not need classifications to start our work on banning a substance globally. This substance has been on the market for more than 50 years, we are lagging too far behind for the regulation on one of the most bioaccumulative PFASs ever known, which by the data from the limited controlled toxicity studies available seems to act in a similar manner as the more investigated PFAS for several adverse effects.</p>
The Netherlands	General comment		<p>From the document, and from the literature, it is clear that there are a lot of measurements on PFHxS, but there are still a lot of uncertainties concerning the substance. And a lot of essential data are lacking. There are no data on production and there is a very scattered picture of the applications of PFHxS, which hampers interpretation. However, the presence of PFHxS in the environment and the lacking of data do not raise any questions in the profile and I think they should be raised. Does the presence of PFHxS in a lot of environmental media really mean that it has been applied a lot, or is it attributable to degradation of precursors. If the authors think that it is applied a lot, why is there no registration in REACH? And, are there any data on production and/or use from other regions? If they think the environmental concentrations can be attributed to degradation of precursors, can the risk profile shed more light on these degradation routes, because the information that has been provided on that until now is very limited?</p>	<p>Comment noted.</p> <p>We agree that there is a lack of data on production of these group of substances. However, identified producers in Italy and China have been contacted in their native language both by email and by phone but they have not been willing to give any information. In addition, 3M as an historical producer have been contacted, without any result. It is in our interest to have as much information available for this risk profile. However, when stakeholders are not willing to give information it is not possible for us to provide this information in the risk profile.</p> <p>We anticipate that the use of PFHxS precursors and contamination in PFOS etc are responsible for much of the PFHxS detected in the environment. However, levels of PFHxS is increasing in some matrixes and regions while levels of PFOS is decreasing. We believe that this is due to intentionally use of PFHxS/PFHxS-precursors. It is a problem that there are no quantitative analytical methods available at</p>

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				<p>present to analyse these PFHxS precursors hence most of the detected levels published so far is on PFHxS. We do believe that the use of PFHxS and its related substances are significant in consumer products and that do indeed point out the weakness in the registration in REACH for substances that are added to products in small amount only.</p> <p>It also says something about not sharing information of chemicals included in/or added on products.</p>															
The Netherlands	General comment		<p>I understand that the drafters want to make their point, but this should not be done by violating the scientific data. In paragraph 61 of the profile they state that the “Results show that after the concentration of PFHxS levelled off during the period 2003 – 2009, the levels are now increasing with an annual increase of PFHxS in polar bears ranging between 4.9 and 5.1%.” However, the data in supporting information of Routti et al (2017), Table S9 show a quite different pattern (see below).</p> <table><tr><th></th><th colspan="2">Polar bear plasma</th></tr><tr><th></th><th>time</th><th>adjusted</th></tr><tr><td>PFBS</td><td>2000-2014</td><td>-</td></tr><tr><td>PFHxS</td><td>2003-2009</td><td>-8.8 (-12.5, -4.8)</td></tr><tr><td>PFHxS</td><td>2009-2014</td><td>4.9 (-1.1, 11.2)</td></tr></table> <p>Firstly, the 4.9% are adjusted data and 5.1% the non-adjusted for Polar bear over the period 2009-2014. Thus, there is NOT a range. Considering the confidence interval provided in the table, I would consider the increase as not significant different from zero!! According to the same data table where the 4.9 and 5.1% are mentioned, the data between 2003 and 2009 showed a decrease of 8.1% and 10.1% on the adjusted data for Polar bear and Arctic fox respectively. I think speaking about a levelling off in the period 2003-2009 and an increase in the subsequent period is providing a wrong reflection of the course of PFHxS concentrations in these species between 2003 and 2014. Looking at the data presented in Table S8 and in Figure 1a of the paper also show a different pattern.</p>		Polar bear plasma			time	adjusted	PFBS	2000-2014	-	PFHxS	2003-2009	-8.8 (-12.5, -4.8)	PFHxS	2009-2014	4.9 (-1.1, 11.2)	<p>The text has been edited and we have been in contact with the author to make sure that we have not misunderstood the data.</p>
	Polar bear plasma																		
	time	adjusted																	
PFBS	2000-2014	-																	
PFHxS	2003-2009	-8.8 (-12.5, -4.8)																	
PFHxS	2009-2014	4.9 (-1.1, 11.2)																	
The Netherlands	General comment		<p>It is not clear how the effect concentrations mentioned in the profile’s sections on toxicity and ecotoxicity relate with the current environmental concentrations and what it means in terms of risk.</p> <p>In a lot of publications, also the ones cited in this risk profile, PFHxS is one of the most abundant PFC. Although, often in a lower concentration than PFOS and/or PFOA. This is not reflected in the document. Some reflections on that, in relation with the comments above</p>	<p>Comment noted.</p> <p>In the INF-document examples on current environmental concentration will be presented, and some of these data do also present levels of PFOS, PFOA and other relevant PFAS for comparison.</p> <p>The relative amount of PFHxS has been reflected in Section 2.3</p> <p>There is no requirement under Annex E to compare and adverse effect. Article 1 of the</p>															

Source of Comment	Page	Para	Comments on the first draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds	Response
			(production, use, degradation) should be on its place in the profile. This could be more highlighted in the text as well as in the summary, e.g. in paragraph 5.	Convention states that "Mindful of the precautionary approach as set forth in Principle 15 of the Rio Declaration on Environment and Development, the objective of this Convention is to protect human health and the environment from persistent organic pollutants." Article 7, paragraph 8 (a) moreover states that "Lack of full scientific certainty shall not prevent the proposal from proceeding."
The Netherlands	6	11	Please be very clear here and use a definition that is crystal clear to everyone. 2. "However, PFHxS salts and other PFHxS related compounds, which can be degraded to PFHxS under environmental conditions and are therefore also known as precursors."	The text has been edited
The Netherlands	6	13PFHxSF- or perfluorobutansulfonyl fluoride (PFBSF)-derivatives will reach more than 1000 tonnes annually worldwide or China?.	Text has been edited
The Netherlands	9	23	Guess POSF in the text throughout the document should be PFOSF ?	No, we use POSF which is the preferred terminology in Buck et al 2011.
The Netherlands			Table 3. Overview of PFHxS, its salts and PFHxS-related compounds manufactured or imported in the US (source: US EPA Inventory Updating Reporting) "What does 'no reports' mean precisely ?"	It means that the "US EPA Inventory Updating Reporting" have not provided any numbers for this substance and year.
The Netherlands	12	29	In relation to business information (SPIN, 2018): Please indicate whether PFHxS has been registered or pre-registered and what the data means in terms of use within the EU:	Information in the SPIN data base states that the substances have been registered in one or more of the Nordic countries. For information about registered or pre-registered within the EU we recommend that you use the ECHA search engine or read the following report "Investigation of sources to PFHxS in the environment (M-961/2018)" that is now referenced in the RP.
The Netherlands	12	30	Data on the constituents of AFFFs have been submitted during the European commenting round on PFHxS by the Mineraloelwirtschaftsverband, Industry or trade association, Germany. That information is publicly available. I would strongly recommend to incorporate that information here, as it will shed some light on the (current) presence of PFHxS and other PFAS substances in AFFF. https://echa.europa.eu/proposals-to-identify-substances-of-very-high-concern-previous-consultations/-/substance-rev/16001/term?_viewsubstances_WAR_echarevs substanceportlet_SEARCH_CRITERIA_EC_NUMBER=206-587-1&_viewsubstances_WAR_echarevs substanceportlet_DISS=true	This information that you are referring to is not easily available through this link. Please summarize the information and submit it in the next comment round.

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The Netherlands	12	30	Literally Olsen et al (2005) state « 3M produced PFHS [perfluorohexanesulfonate] as a building block for compounds incorporated in fire-fighting foams and specific postmarket carpet treatment applications » Thus, it is not correct to add the word ‘-related’ in this case.	Text has been edited.
	12	31	In relation to: “process to produce electronic devices, does this refer to the semiconductor industry?	The text reflects what is written on the EPA web page.
The Netherlands	12	32	Similar remark as above on AFFFs	No changes “have been made. Although 3M states that PFHxS has been used as building blocks in AFFF, PFHxS related compounds have been detected in historical 3M AFFF. See section 2.2.2 PFHxS precursors and degradation
The Netherlands	13	37	Please find enclosed the permit for Agfa Gevaert comprising PFOS, PFOA and PFHxS : https://www.milieuinfo.be/dms/d/a/workspace/SpacesStore/706b0fc2-ca0f-4c9d-9367-5c8306a0a420/MLAV1-2014-0314.pdf The permit also contains quantitative information.	This document is provided in Dutch only, for transparency reasons it cannot be used unless it is translated into English.
The Netherlands	13	39	What is the proper reference if this statement ? skeleton is twisted out of its plane in the form of a helix and this structure shields it from chemical attack.	Siegemund et al., 2000 as referenced in ECHA 2017a
The Netherlands	14	41	1) Braunig et al does not contain anything on degradation of PFHxS. Please use a proper reference. 2) Filipovic et al does not contain anything on degradation of PFHxS as well. Please use proper reference 3) Both publications indicate the presence of various PFAAs in soil close to a AFFF training site or an airport. In both cases PFOS is being detected followed by PFHxS. undergo any abiotic or biotic degradation under normal environmental conditions (Braunig et al., 2017; Filipovic et al., 2015).	The text in this paragraph has been edited by others. However, the text does not state that Braunig et al and Filipovic et al have performed any degradation experiments. The references are there to stress that PFHxS is still highly detectable after historical use of AFFF. This argument for PFHxS persistency was brought forward by POPRC13.
The Netherlands	14		In relation to 2.2.2 PFHxS degradation and precursors: One big question that remains after reading this chapter is whether experimental data on the degradation to PFHxS are present. If yes, please add, if not, please indicate that in the text.	The text has been edited.
The Netherlands	14	43	The authors of the Norwegian study warn at the end of the report : The extremely scarce literature on abiotic degradation of compounds	The assessment is theoretical and that is clearly stated in the risk profile and in the report itself. It is also stated in the text that

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			such as CF ₃ (CF ₂) _n S(O ₂)N-R, CF ₃ (CF ₂) _n S(O ₂)O-R and CF ₃ (CF ₂) _n S(O ₂)-R, warrants that systematic research on these classes of compounds is undertaken such that their fate in the environment can be modelled in a scientific manner.	no degradation studies are available. There is no need to further stress this in the text.
The Netherlands	14	44	Question is what the authors want to say by this sentence (see below)? Although in fact, the sentence is right, it suggest that PFHxS can hardly be measured. The number of publications on PFHxS and other fluorinated substances indicate that these are measured in a lot of places. Analytical methods for identifying and quantifying PFHxS-related compounds (e.g. FHxSA) are at present very limited.	No. What this sentence is saying is that "Analytical methods for identifying and quantifying PFHxS-related compounds (e.g. FHxSA) are at present very limited." Methods for identifying and quantifying PFHxS is highly available.
The Netherlands	14	45	In relation to surface (and ground) waters: Meyer et al 2011 remark : Run-off behavior was clearly dependent on per fluoroalkyl chain length: Dilution with relatively clean snowmelt water caused a drop in the river water concentrations of short-chain PFCs at high flow during early melting	Comment noted. The point under this section is rather the fact that PFHxS is detected in snow and that could be due to air transport of PFHxS precursors that could have degraded to PFHxS in the snow.
The Netherlands	15	Table 5	The text below is taken from the annex XV dossier for REACH by the Swedish Chemical Agency (2017). Cited in this profile as ECHA 2017a. It would be good to take account of the remarks below and reflect that in the text of the profile. "Problems arise with increasing body size of predators because analysis is based on tissue or serum samples. This is especially true for organisms at the higher trophic levels (e.g., polar bear), while it is feasible to measure the whole-body on smaller species at lower trophic levels. Whole-body analysis is not feasible for ethical reasons, i.e. a whole whale would be needed, and due to the challenging logistics with respect to sampling and laboratory constraints. Therefore, some of the derived BMF-values are restricted to certain tissue samples rather than whole body samples. Whole body values may be estimated if the tissue mass fraction is known for the organism regarded. There may however be some uncertainties due to inter individual and geographical differences but these uncertainties cannot be quantified ((Houde et al., 2006)). BMF values based on liver samples may be overestimated. From a toxicological perspective, concentrations in individual organs, such as the liver, may be more relevant when the potential for direct organ-specific toxicity (i.e., liver toxicity) is predicted."	Some text has been added and the ECHA 2017 dossier on PFHxS has been cited. The information you are referring to is of mostly general nature. <ul style="list-style-type: none"> • whole body/ tissue specific bioaccumulation calculations • time and location of sampling • Accumulation in fat contra protein-bond substances • etc <p>This has been discussed at several POPRC meetings hence we don't think it is necessary to elaborate around this here since we have a page limit of 20 pages. We also discussed the limitations of some of the BMF/TMF studies in the nomination dossier.</p> <p>No data has been removed and bioaccumulation is reviewed using weight of evidence and all the data considered, we conclude that there is enough evidence to state that PFHxS is bioaccumulating.</p>
The Netherlands	15	Table 5	Butt et al 2008 make a similar remark: Because PFCs have been shown to accumulate preferentially in proteinous	See comments above

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			<p>tissues, such as liver and plasma, biomagnification may have been overestimated. For example, in a bottlenose dolphin food web, BMFs calculated using liver concentrations were up to 30-fold higher than those calculated using whole-body values [65].</p> <p>A further remark on Butt et al 2008 is on its place: "Perfluorobutane sulfonate was not detected, whereas PFHpA, PFHxS, and perfluorodecane sulfonate were measured infrequently (less than 25%) above the MDL (method detection limit)."</p> <p>Followed by the following remark in the Butt et al 2008 paper: " For calculation of means, the concentrations less than the MDL or nondetect were replaced by a random number less than half the MDL".</p> <p>Thus, a big questionmark can be added to the values of 163-373 in Table 5. I would recommend to skip these values from the table and also from the summary text.</p>	
The Netherlands	17	56	<p>Please add reference or argumentation:</p> <p>....A number of studies show evidence that PFAS precursors are transported through air and degrade to e.g. PFBS, PFOS (Stock et al., 2007; Dreyer et al., 2009; Del Vento et al., 2012) and most likely also PFHxS.</p>	The text has been edited and references have been added.
The Netherlands	17	58	<p>For the sentence below: See the RIWA 2016 report that has been submitted by The Netherlands in December. The data in the various RIWA reports also enable to make a comparison of the amounts of the various PFAS substances.</p> <p>Numerous studies have reported detection of PFHxS in compartments such as surface water, deep-sea water, drinking water, wastewater treatment plant, sediment, groundwater, soil, atmosphere, dust, biota, and humans globally (ECHA 2017a, Annex II table 13; Table XX in POPRC14/INF/XX).</p>	<p>We are not sure which of the Dutch submitted reports are the RIWA 2016 report? Furthermore, a few of the Dutch submissions are in Dutch and for transparency reasons (and the lack of the drafters' knowledge of Dutch) it cannot be used.</p> <p>We refer to the POPRC14/INF/XX document for detected levels in various matrixes.</p>
The Netherlands	17	59	<p>In relation to the last line: Can degradation of PFOS be excluded as source? Paragraph 43 notes that PFOS almost solely biodegrades to PFHxS, but does not indicate how fast/readily this occurs.</p>	<p>YES. PFOS does not degrade to PFHxS.</p> <p>Text in para 43 has been modified.</p>
The Netherlands	17	61	<p>The data in Routti et al (2017) show that 4.9% are adjusted data and 5.1% the non adjusted for Polar bear. Thus there is NOT a range and it would be good to mention Polar bear here !</p> <p>Considering the confidence interval provided in the table, the increase is not significant different from zero !!</p> <p>According to the same data table where the 4.9 and 5.1% are mentioned, the data between 2003 and 2009 showed a decrease of 8.1% and 10.1% for Polar bear and Arctic fox</p>	Text has been modified. We have been in contact with the author and she has agreed on the text that is now present in the RP regrading this study.

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			<p>respectively. I think speaking about a levelling off in the period 2003-2009 and an increase in the subsequent period is providing a wrong reflection of the course of PFHxS concentrations in these species.</p> <p>Results show that after the concentration of PFHxS levelled off during the period 2003 – 2009, the levels are now increasing with an annual increase of PFHxS in polar bears ranging between 4.9 and 5.1%.</p>	
The Netherlands	18	62	Please have a proper look at table S9 in Routti et al 2017 and the remark to paragraph 61. It is also in contradiction with the text in Routti et al 2017 page 12002.	The text has been modified but not deleted
The Netherlands	19	70	<p>Please explain in a way that it is understandable. Now the two last sentences convey an opposite message.</p> <p>" In a Swedish monitoring study, PFHxS was analysed in breast milk samples from Stockholm and Gothenburg. The concentrations of PFHxS, (low pg/mL range), have increased over the whole time-period (1972-2015) in Stockholm, though there seemed to be a decrease during the last 10 years both in Stockholm and Gothenburg (Nyberg et al., 2017"</p>	Sentence has been edited.
The Netherlands	20	76	Comment to the study Lou et al., 2013: Essential here is whether the effects can be attributed to PFHxS or whether they are due to 100 and 1000 ug/L PFOS. If it is not possible to distinguish, please skip this sentence.	<p>We prefer to keep it in due to lack of relevant studies of PFHxS to aquatic organisms. We believe toxicity studies which include both the C8 and C4 sulfonate can help to picture the expected toxicity of C6-sulfonate.</p> <p>It is clearly written that it is PFOS and PFBS which cause the effects. However, for the PFOS exposure one cannot exclude potential effects from the small amount PFHxS present, but it is more likely that PFOS contribute more.</p> <p>The units are corrected for the sentence as it had fallen out.</p>
The Netherlands	20	76	<p>Please keep the text to PFHxS. This sentence is not about the substance to nominate.</p> <p>"From other laboratory studies, PFOS is known to be moderately acute and slightly chronically toxic to aquatic organisms and the few PFBS studies available indicate lower toxicity of PFBS (Ding and Peijnenburg, 2013; Giesy et al., 2010)."</p>	We prefer to keep it in due to lack of relevant studies of PFHxS to aquatic organisms. We believe a general statement on toxicity of the C8 and C4 sulfonate can help to picture the expected toxicity of C6-sulfonate.
The Netherlands	21	82	Please use similar units throughout the risk profile	Will do in the next version.
The Netherlands	22	88	<p>Comment on first sentence:</p> <p>Firstly, the first sentence suggest that Jain et al (2013) focus on endocrine effects. The authors do not mention endocrine effects in their paper.</p>	Thyroid hormone is indeed a part of the endocrine system, and effects on TH system can be put into the discussion about

Source of Comment	Page	Para	Comments on the first draft of the risk profile on Perfluorohexane sulfonic acid (PFHxS), its salts and PFHxS-related compounds	Response
			Secondly, the sentence speak about endocrine-disrupting effects have been shown, but Jain et al only show an association between PFAA levels and certain parameters as the title of the publication reflect.	endocrine effects. No change made to the text.
The Netherlands	23	2.2.4	<p>Jain et al 2013, cited in the previous paragraphs, provides some consideration in their study on the multiple effects. Such critical considerations are completely lacking in the following paragraphs.</p> <p>Jain et al., 2013 : In this study, the influence of one FAA variable at a time was evaluated with each of the six thyroid function variables. It may be of interest to study the combined effect of all six PFAA variables on each of the thyroid variable. Mechanically, it should not be difficult because instead of as single PFAA variable, all six PFAA variables could be used simultaneously as covariates in the regression models. However, this will mean any result ant effect on, for example, TSH, has been adjusted for the inter-correlations between the six PFAA variables. This, depending upon the size of the correlations between PFAA variables may trigger multicollini- nearity in the model. If so, some of the PFAA variables which may have statistically significant effect on, for example, TSH may be rendered statistically non-significant. Hence, the simultaneous use of multiple PFAA should be done with caution and certain amount of reservations.</p>	<p>Comment noted, no chance was made to the text due to the page limit.</p> <p>In this section controlled laboratory experiments dealing with mixtures were included.</p> <p>For the field and epidemiology studies included, we trust the POPRC members to know the complexity of these studies, as all organisms including humans are exposed to a complex cocktail of chemicals, but also at the same time remember that this particular substance is extremely bioaccumulative in certain organisms.</p> <p>All literature referred to concerning toxic effects are peer-reviewed.</p>
The Netherlands	24	96	In relation to the last two sentences: The risk profile is on PFHxS. Please keep statements in this paragraph to PFHxS or leave it away.	<p>Comment noted and reference added, however, this is a feature PFHxS and other PFASs share.</p> <p>“Certain” was added before PFASs to more precisely reflect that some PFASs do biotransform (to PFCA or PFSA).</p>
The Netherlands	24	99	<p>It is not clear what this information add to the profile?</p> <p>See Norwegian Environment Agency (2017a).</p> <p>While analytical methods for detection of PFHxS are well established, it is presently a challenge to qualify and analytically quantify PFHxS precursors. However, precursors such as perfluorohexane sulfonamides were detected/identified in leachates from landfills indicating that these PFHxS precursors may be used in a variety of applications since the landfills had received waste from a number of sources. FHxSAs has also been detected in historical AFFF manufactured by 3M.</p>	<p>No changes have been made to the text. We believe that it is important to stress that there is a lack of quantitative analytical methods that allow detection of the PFHxS precursors. Hence, there might be a number of PFHxS precursors present in a variety of matrixes that are not detected due to lack standardized detection methods.</p> <p>Norwegian Environment Agency (2017a) is referenced where appropriate.</p>
The Netherlands	24	102	The sentence is factually incorrect. The transfer through the placenta has nothing to do with breast feeding.	Sentence rephrased

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The Netherlands	25	104	Suggestion to make this more general by referring to cocktail effects with traditional POPs in fat storage according to paragraph 96. Organohalogens can then serve as an example.	Text has been edited.
Canada		General	Many minor edits or proposed changes	Many of these have been accepted, but are not listed in this Table
Canada	2	1	compounds, which is any substance that contains the chemical moiety [C ₆ F ₁₃ SO ₂] as one of its structural elements and has been shown to that or potentially.....	No changes made. It has not been experimentally shown that PFHxS precursors degrade to PFHxS. However, degradation has been shown for PFBS and PFOS.
Canada	2	6	In relation to increased emissions: Suggest to specify if it is due to an increase of local emissions or from international sources.	Text has been edited. Routti et al states that the increased levels observed is due to increased emission through water currents (the water volume has increase the last 2 decades). However some influence of local sources cannot be completely excluded but there is to date no good method to distinguish between local transport and long-range transport.
Canada	2	6	In relation to PFHxS and its volatile precursors: Suggest to specify which volatile precursors	No changes made. It is PFHxS that has been detected in matrixes (air, rain, snow melt water) that might have contained (due to air transport) precursors that have degraded to PFHxS.
Canada	4	13	Suggest, if data available, to breakdown in tonnage between the hexane and butane substances. This relates to end of paragraph ... will reach more than 1000 tonnes annually.	No such data available.
Canada	6	20	Consider to delete as the intent of this paragraph is to indicate which countries have already taken action. The Canadian Domestic Substances List (DSL) is a list of substances manufactured in, imported into or used in Canada on a commercial scale. It is not a priority list.	No changes made. This section summarizes available status from countries. In EU and Norway i.e. also no action has been taken.
Canada	10	32	Suggest to continue with the acronym PFHxS as C-6, even if commonly used in reference to perfluorohexanoic acid, could introduce confusion due to its multiple uses.	No changes made. We prefer to use the language used in the peer-reviewed paper.
Canada	13	2.2.3	Bioaccumulation.... Suggest, as per the toxicity section, to separate between aquatic organisms and terrestrial mammals (including humans)	No changes made. We're not sure how much value this will add to the document at this point. This will take quite a bit of time and we are under a time-pressure to address all the comments of the intersessional working group.
Canada	16	61	Add as a new 2 nd last paragraph: In polar bears from East Greenland and in samples collected in 2006, a tissue distribution study should that levels of PFHxS were highest in the liver followed by blood > brain ≈ muscle ≈ adipose (Greaves et al. 2012), but consistently 2 orders	This text has been included.

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			of magnitude lower than PFOS. In a complementary study in various brain regions of the same polar bears, PFHxS concentrations were consistently the same throughout the brain (Greaves et al., 2013).	
Canada	17	68	Please rephrase to: Concentrations of PFHxS in maternal blood were negatively associated with parity and maternal age and positively associated with income. Current smokers showed higher geometric mean PFHxS concentrations than former, or never smokers and foreign-born mothers had lower PFHxS levels than Canadians (Fisher et al. 2016).	Text has been edited.
Canada	18	76	Comment on <i>Rana pipiens</i> : First time that latin names are used. Suggest to remove or add the latin names throughout the text for consistency.	We want to keep it in this section as some readers might be more familiar with the Latin names of some of these amphibians.
Canada	18	77	Suggest to rephrase to avoid repetition: The exposure caused hepatomegaly with steatosis as well as reduced serum total cholesterol and triglycerides mainly by impairing lipoprotein production.	The sentence has been rephrased
Canada	19	83	Suggested wording for accuracy as exposure was from 8.9 ng/g, but changes were observed at a concentration 10x higher.	Clarification included.
Canada	20	87	Insert details on study: In a cross-sectional analysis of adults from cycle 1 (2007-2009) of the Canadian Health Measures Survey (CHMS), And correct results: LDL-cholesterol, non-HDL, HDL/TC ratio	Sentences have been rephrased. However, we believe the author referred to TC/HDL ratio as this ratio is used in the materials and methods and the table.
Canada	21	90	Suggest to specify in “relation to high concentrations of PFHxS?” for the Grandjean 2012 study	Added specification used in the study.
Canada	21	90	Please add: In contrast, a Canadian study of prenatal exposure to PFHxS and cord blood immune markers (IgE, IL-33, TSLP) reported no significant associations (Ashley-Martin et al, 2015).	Text has been added.
Canada	22	96	For last sentence: Consider to include in which species	Text has been edited
Jamaica		21	Please consider the following edit. “... Responses from participating countries indicated that risk reduction approaches for PFASs are mainly covered under existing national and/or regional regulatory frameworks and cover principally long chains -chain PFASs and their precursors and salts.”	Edited.

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Jamaica		22	Please consider replacing “same parent compound” with “corresponding sulfonyl fluoride”	Text has been edited due to other comments.
Jamaica		23	Please consider the following two edits. “In addition, PFHxSF may be unintentionally produced from the electrochemical fluorination of octanesulfonyl fluoride or chloride, the process to produce perfluorooctane sulfonyl fluoride (POSF) as a byproduct (Gramstad and Haszeldine, 1957). Unless manufacturers remove PFHxSF from POSF, it would stay in POSF and also react with reactants to form PFHxS, its salts and/or PFHxS-related compounds as byproducts in formation of PFOS and its related compounds, as shown in, e.g., 3M (2015), Herzke et al. (2012) and Huang et al. (2015). It is likely that the yields of PFHxSF and POSF in the production of POSF are between 4% (Gramstad and Haszeldine, 1957) and 14.2% (reported by a Chinese manufacturer, Ren, 2016). “	Text has been edited.
Jamaica		Table 3	The title of the table suggests that data for PFHxS should be included, but there is none; possibly the title should be changed. The CAS number of the second entry corresponds to PFHxS potassium salt	Text has been edited.
Jamaica		29	In the following sentence I think C_nF_{2n-} should be C_nF_{2n+1} . “Due to the thermal and chemical stability as well as the hydro- and oleophobicity of the perfluoroalkyl moiety (C_nF_{2n-}), PFHxS, its salts and PFHxS-related compounds can be used as effective surfactants and/or surface protectors.” Please consider the following edit in the last sentence. “Furthermore, it should be noted that information on the volumes and uses of many PFHxS, its salts and many PFHxS-related compounds has been reported to the competent authorities in Denmark, Sweden and Norway, but most of such information has been claimed as confidential business information (SPIN, 2018).”	Edited.
Switzerland	2	6	One may want to specify if this relates PFHxS or PFHxS-related compounds (or both): ...to increased emissions.	The statement reflects PFHxS emissions. It is not possible to say anything about increased emission of PFHxS precursors since there is no analytical method available to quantify PFHxS precursors. PFHxS is analysed in the actual study.
Switzerland	4	12	Isn't this the case for PFHxS-related compounds, too? PFHxS is present in some fire	Yes most likely, but not analysed in many products (see comment above). Detection of PFHxS precursors in AFFF is reflected elsewhere in the document.

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Switzerland	6	Table 2	I consider it important to demonstrate that PFHxS is a very strong acid, i.e. in an aquatic environment only the anionic form is present.	Table edited.